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Application of neuroimaging to understand rare genetic disorders

Dr Kate Baker, Programme Leader Track and Honorary Consultant

COGNESTIC 27 September 2023

Outline

1. Introduction to an applied neuroimaging challenge
2. Discussion of opportunities and constraints
3. 1 project, 11 years (other examples exist)
4. Ideas for possible future directions

1. Introduction

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Intellectual disability

DSM-V (APA, 2013)

1. Cognitive impairments
2. Adaptive functioning
3. Onset during development

Typically IQ < 70 = 2.5% (1-3%)

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Intellectual disability

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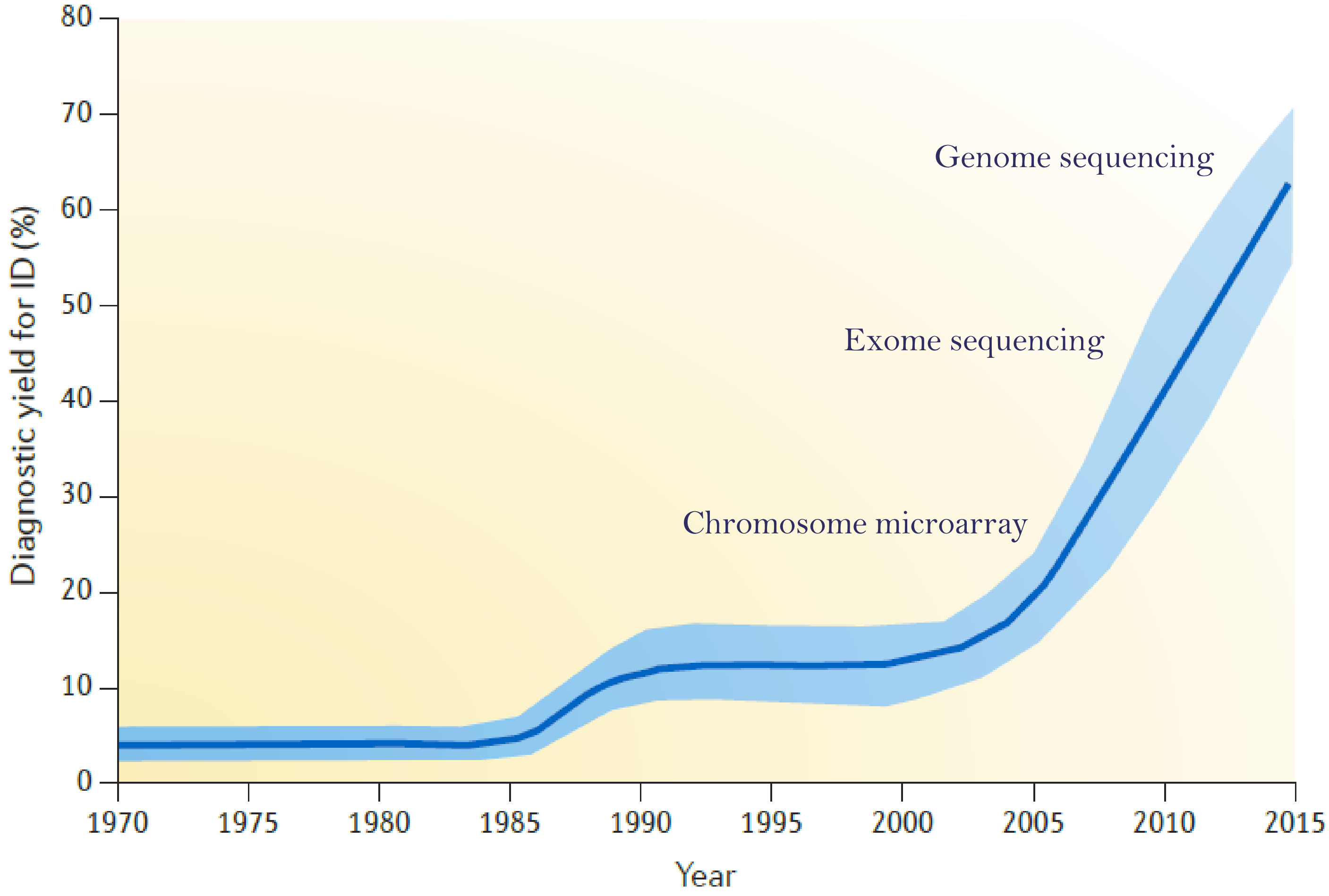
Diversity

- Cognitive profile
- Adaptive impact
- Developmental trajectory
- Associated characteristics
  - Neurological heath
  - Physical health
  - Mental health
- Neurobiology
- Social and cultural context
- Aetiology

Genetic Diagnosis in ID – past, present…



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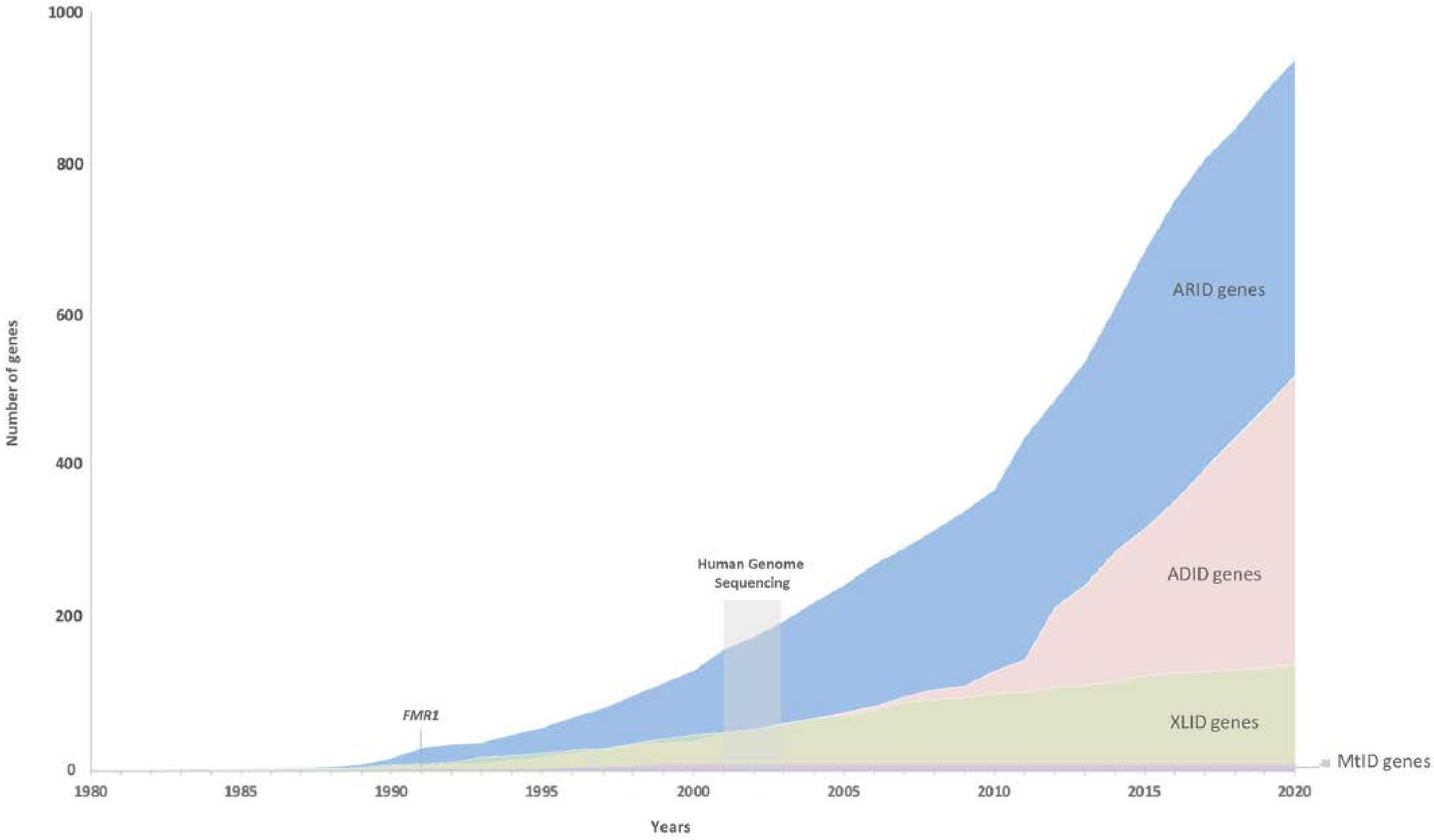
Vissers et al, Nature Reviews Genetics, 2016

Genetic Diagnosis in ID – past, present…



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Maia et al, BMC Genomics, 2021

Opportunity

DSM-V (APA, 2013)

1. Cognitive impairments
2. Adaptive functioning
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Typically IQ < 70 = 2.5% (1-3%)

Diversity

- Cognitive profile
- Adaptive impact
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2. Discussion

A. What are the cognitive neuroscience questions arising from genetic diagnosis in ID?
B. How can neuroimaging address these questions?
C. What are the constraints?

3. One example

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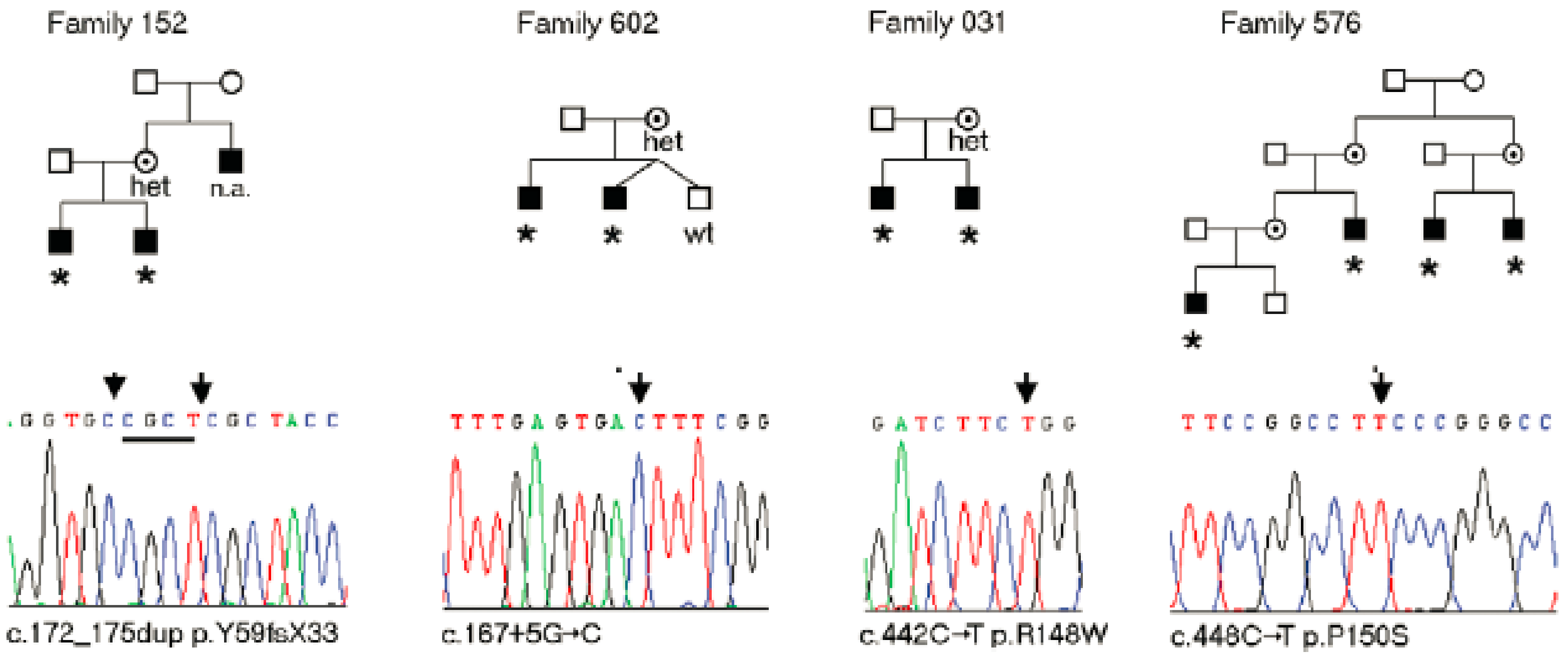
REPORT

The American Journal of Human Genetics Volume 80 May 2007

Mutations in *ZDHHC9*, Which Encodes a Palmitoyltransferase of NRAS and HRAS, Cause X-Linked Mental Retardation Associated with a Marfanoid Habitus

F. Lucy Raymond,* Patrick S. Tarpey,* Sarah Edkins, Calli Tofts, Sarah O'Meara, Jon Teague, Adam Butler, Claire Stevens, Syd Barthorpe, Gemma Buck, Jennifer Cole, Ed Dicks, Kristian Gray, Kelly Halliday, Katy Hills, Jonathon Hinton, David Jones, Andrew Menzies, Janet Perry, Keiran Raine, Rebecca Shepherd, Alexandra Small, Jennifer Varian, Sara Widaa, Uma Mallya, Jenny Moon, Ying Luo, Marie Shaw, Jackie Boyle, Bronwyn Kerr, Gillian Turner, Oliver Quarrell, Trevor Cole, Douglas F. Easton, Richard Wooster, Martin Bobrow, Charles E. Schwartz, Jozef Gecz, Michael R. Stratton, and P. Andrew Futreal



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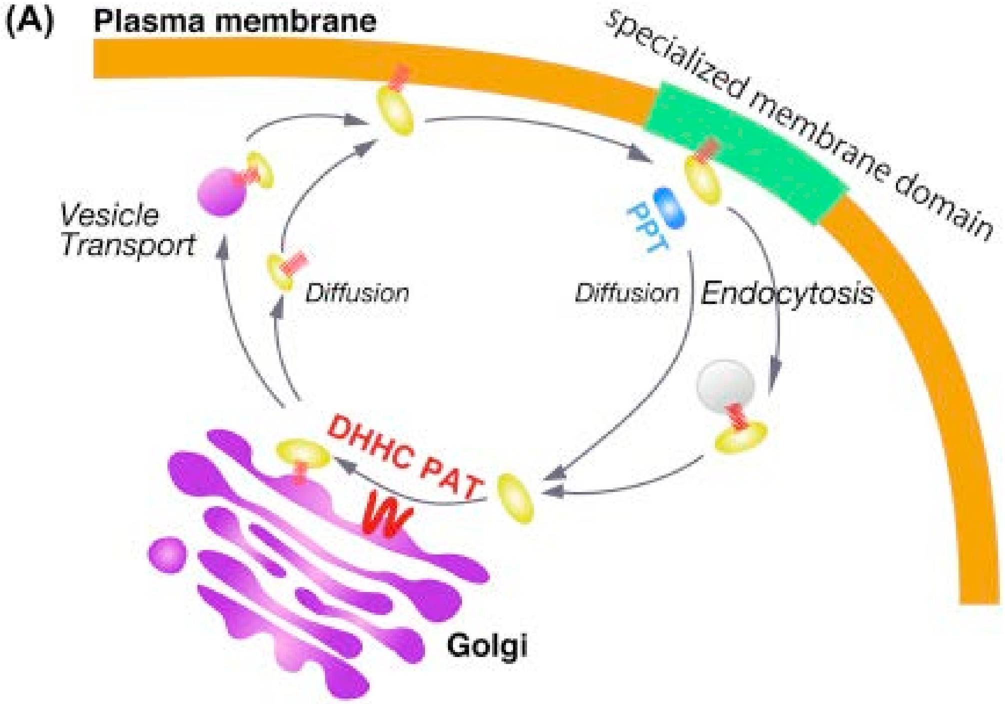
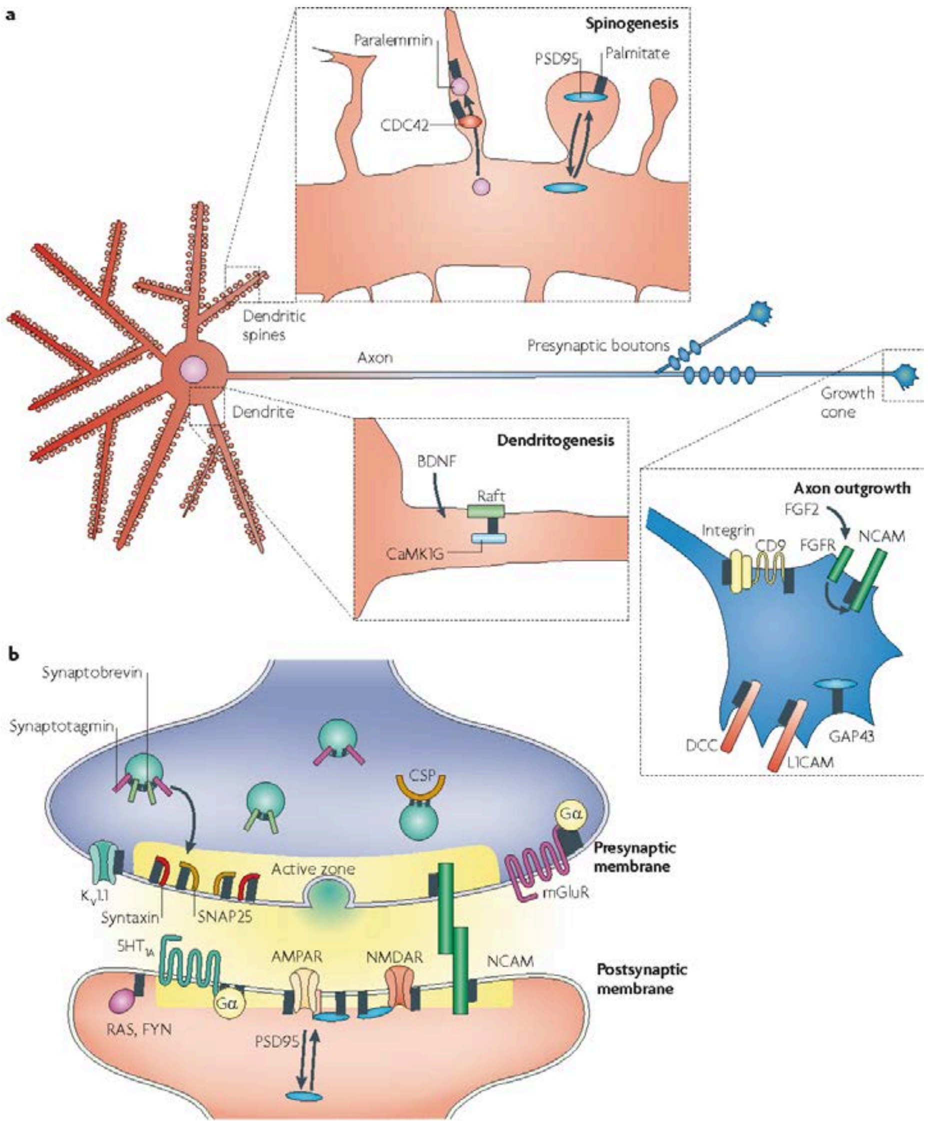
Sciences U

ZDHHC9 functions



Fukata, Yuko, Murakami, Tatsuro, Yokoi, Norihiko, & Fukata, Masaki. (2016). Current Topics in Membranes (Vol. 77, Dynamic Plasma Membranes - Portals Between Cells and Physiology). Elsevier.



Fukata Y1, Fukata M. (2010) Nat Rev Neurosci. Protein palmitoylation in neuronal development and synaptic plasticity.

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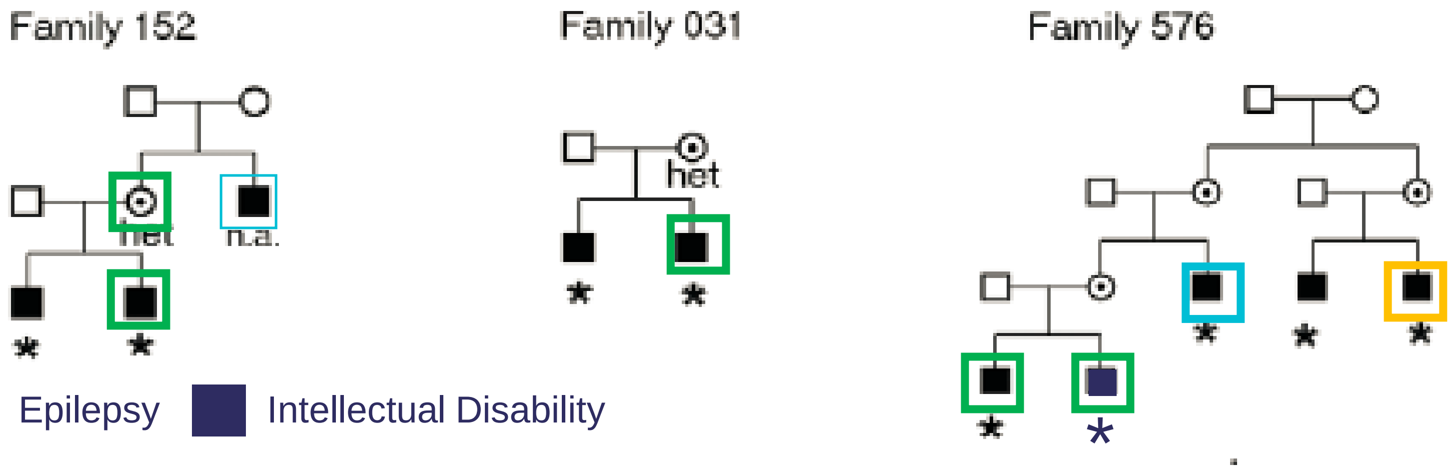
ZDHHC9-associated XLID: Neurology

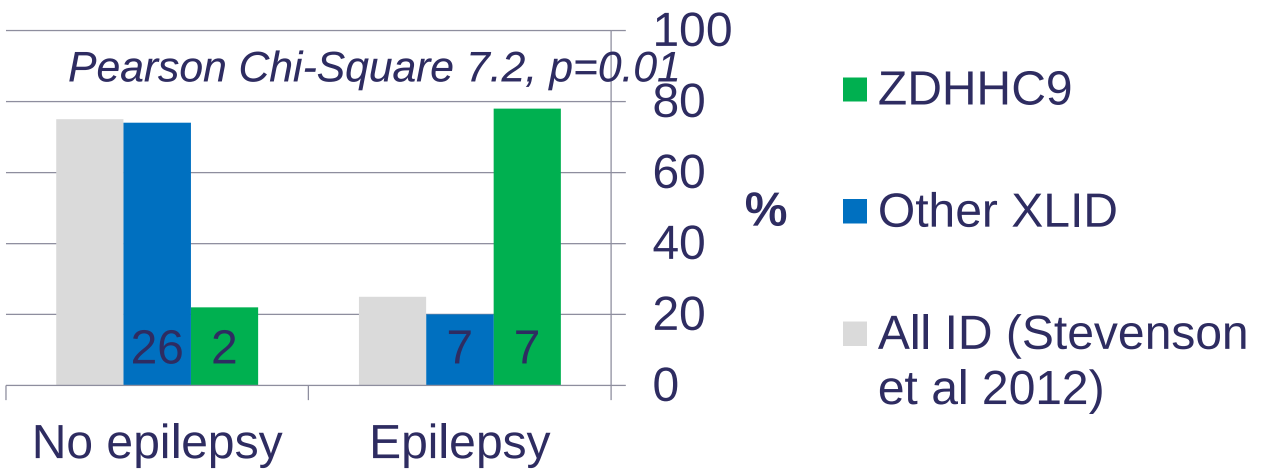


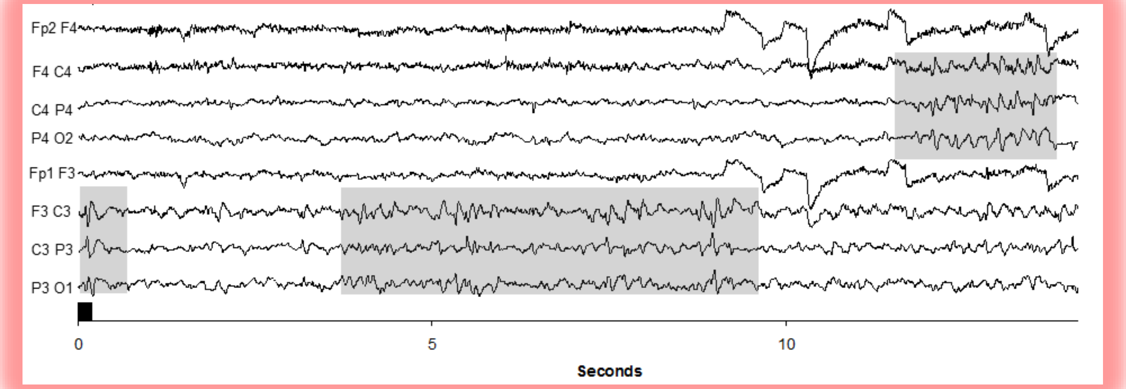
Childhood focal seizures, night, oromotor

Childhood focal + generalised seizures

Adult-onset focal seizures, night, oromotor

Epilepsy   Intellectual Disability





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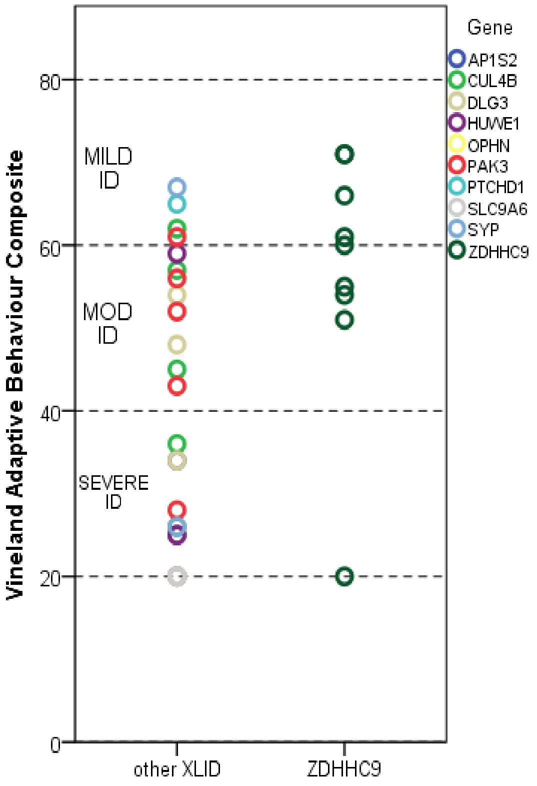
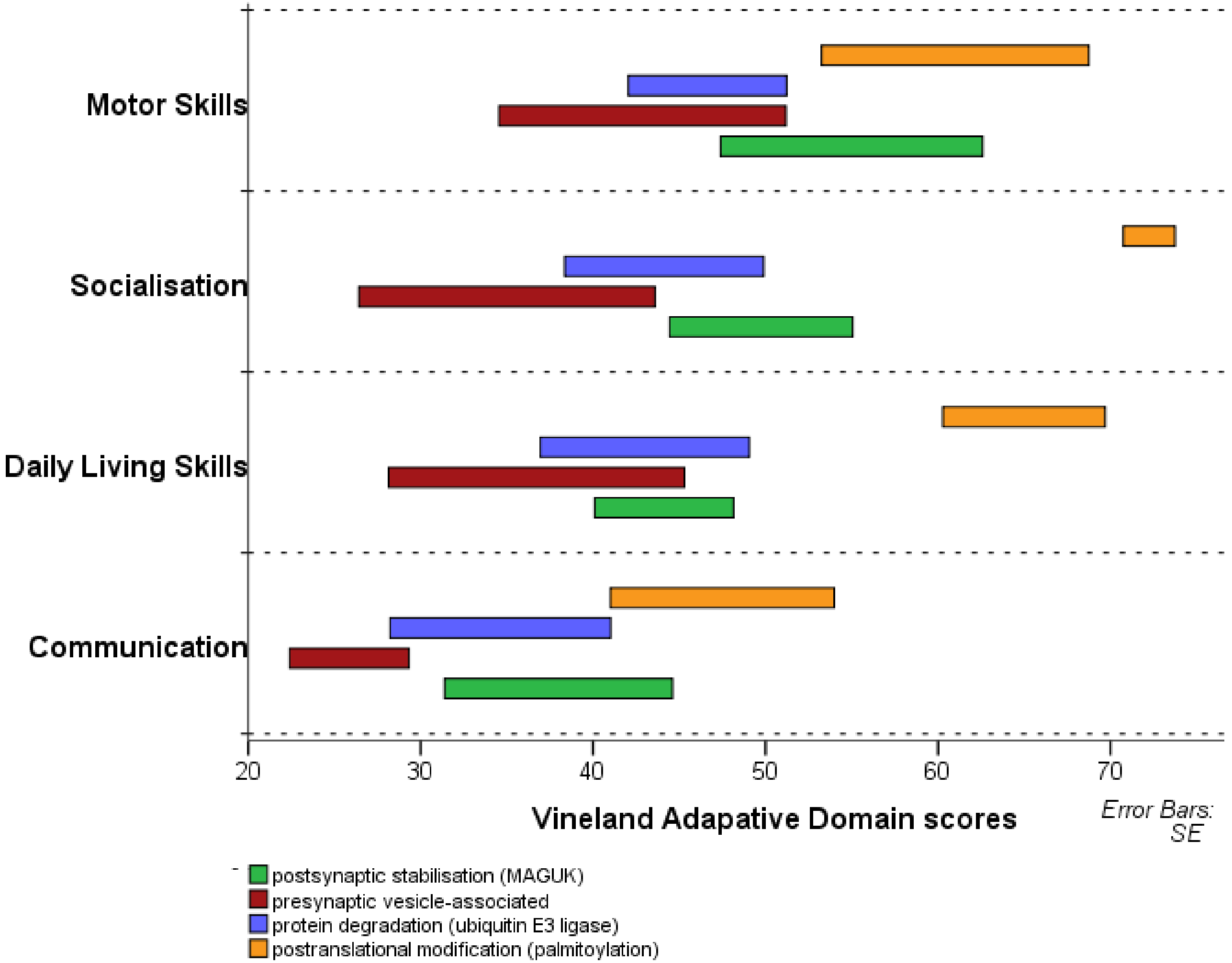
ZDHHC9-associated XLID: Adaptive function

Global ability



Functional domains



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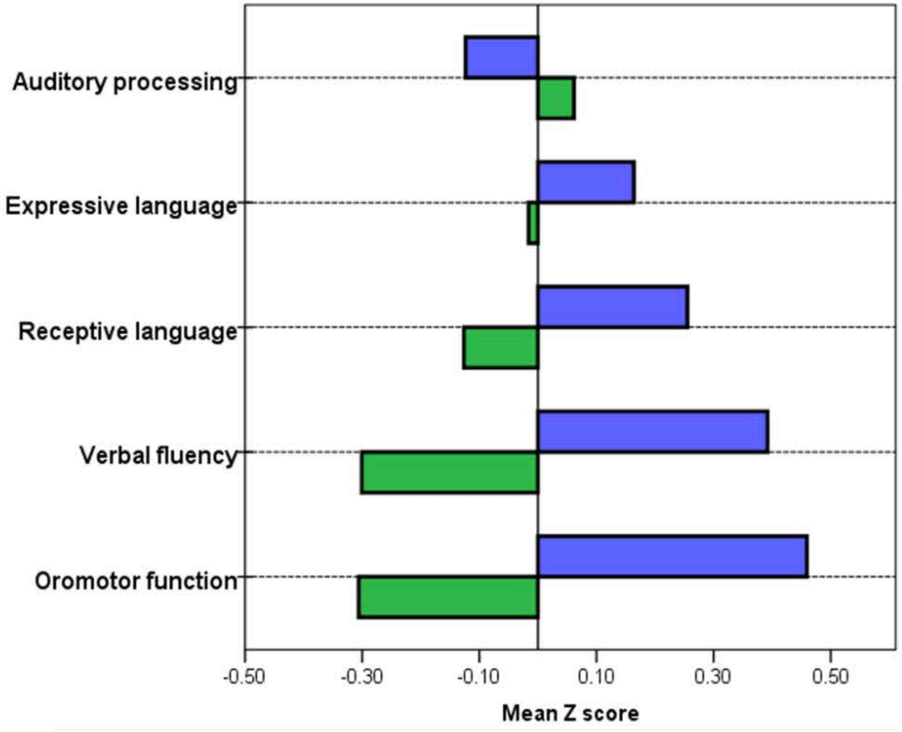
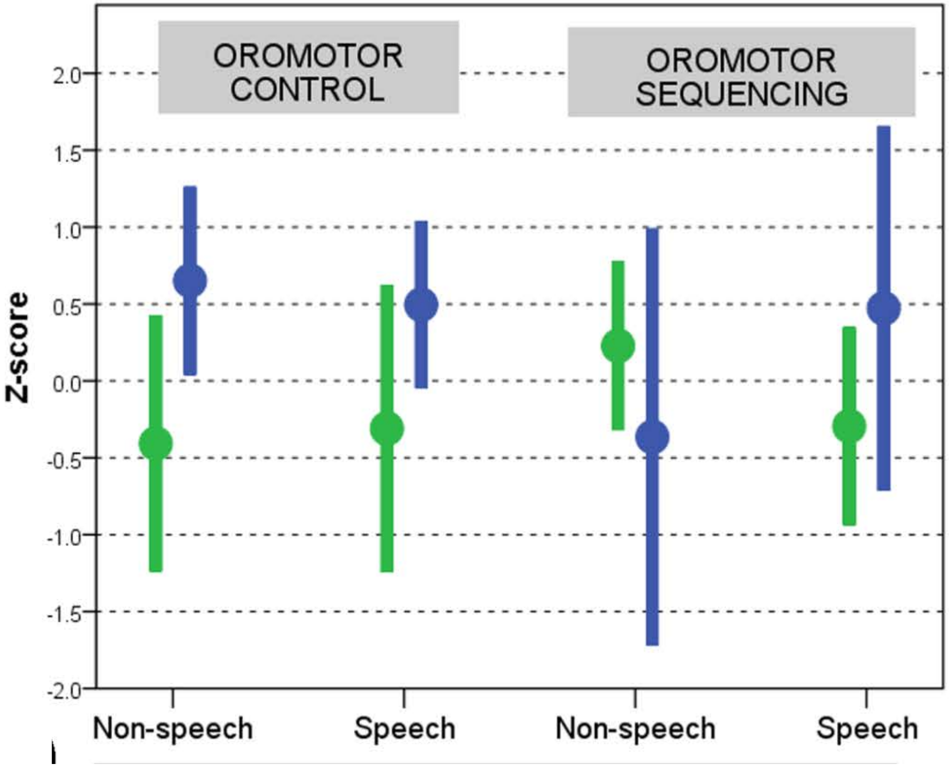
ZDHHC9-associated XLID: Language tests

Standardised language test battery



Verbal Motor Production Assessment



Key: XLID control group *ZDHHC9* group Error bars: 95% confidence interval

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ZDHHC9-associated ~~XLID~~ RE and DLD

What neuroimaging questions would you ask?

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ZDHHC9-associated ~~XLID~~ RE and DLD

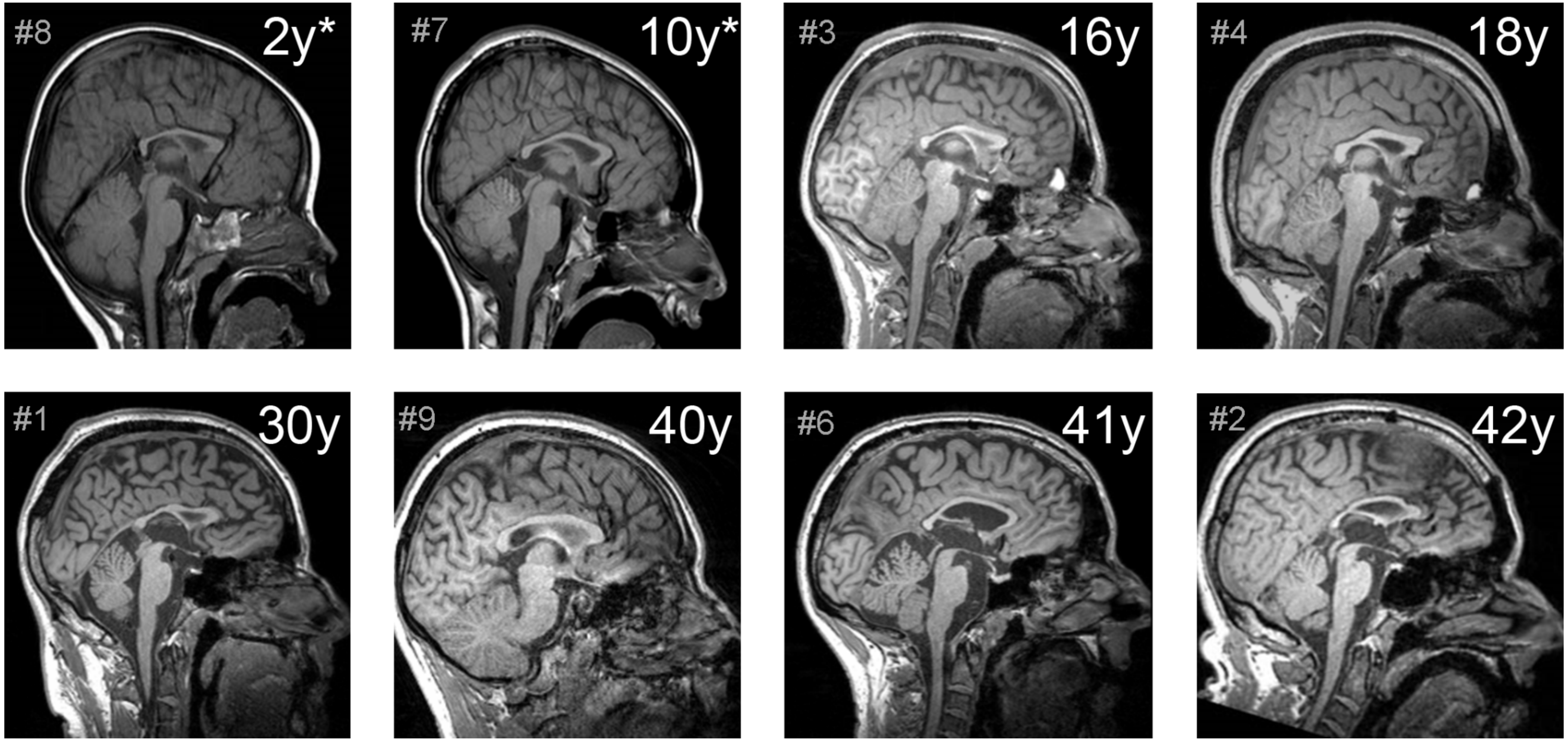
How is brain ~~development~~ structure and function altered?

How does this relate to communication difficulties?

How does this relate to ZDHHC9 expression?

Prediction from RE literature = we won’t find anything much

ZDHHC9-associated XLID: Neuroradiology



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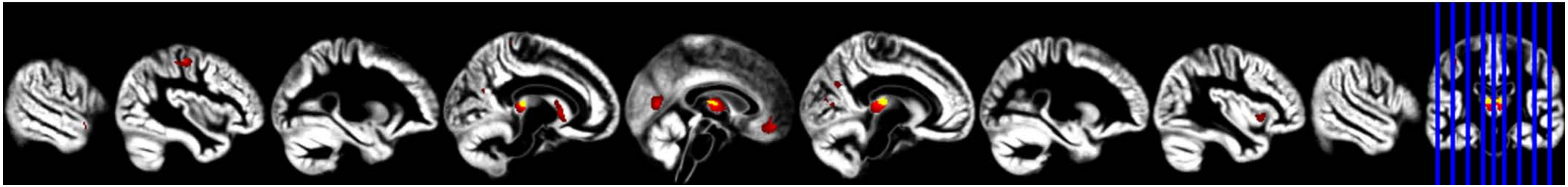
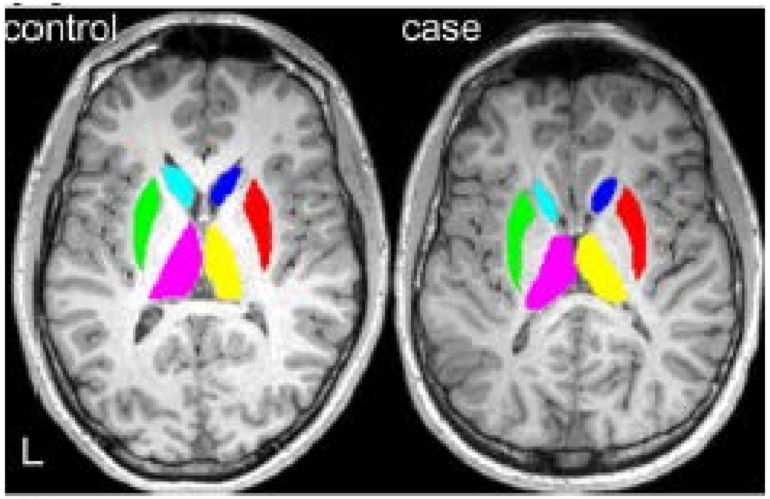
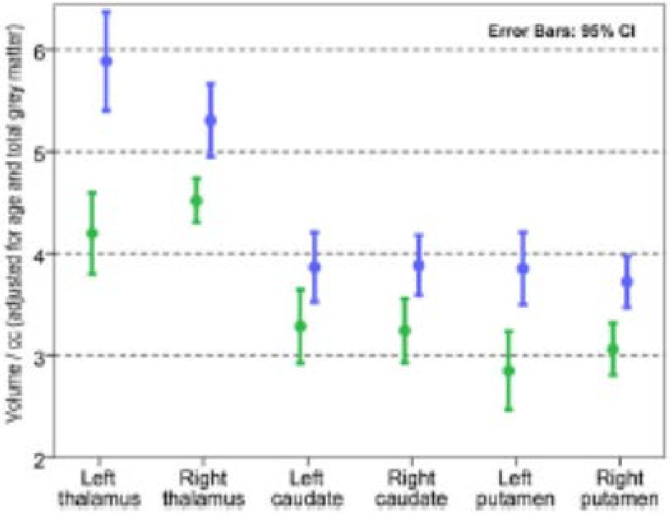
ZDHHC9-associated XLID: VBM

A) Grey matter: cases (n=7) < controls (n=7)







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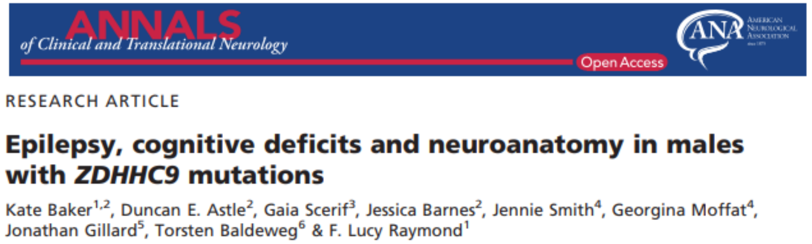

ANNALS of Clinical and Translational Neurology

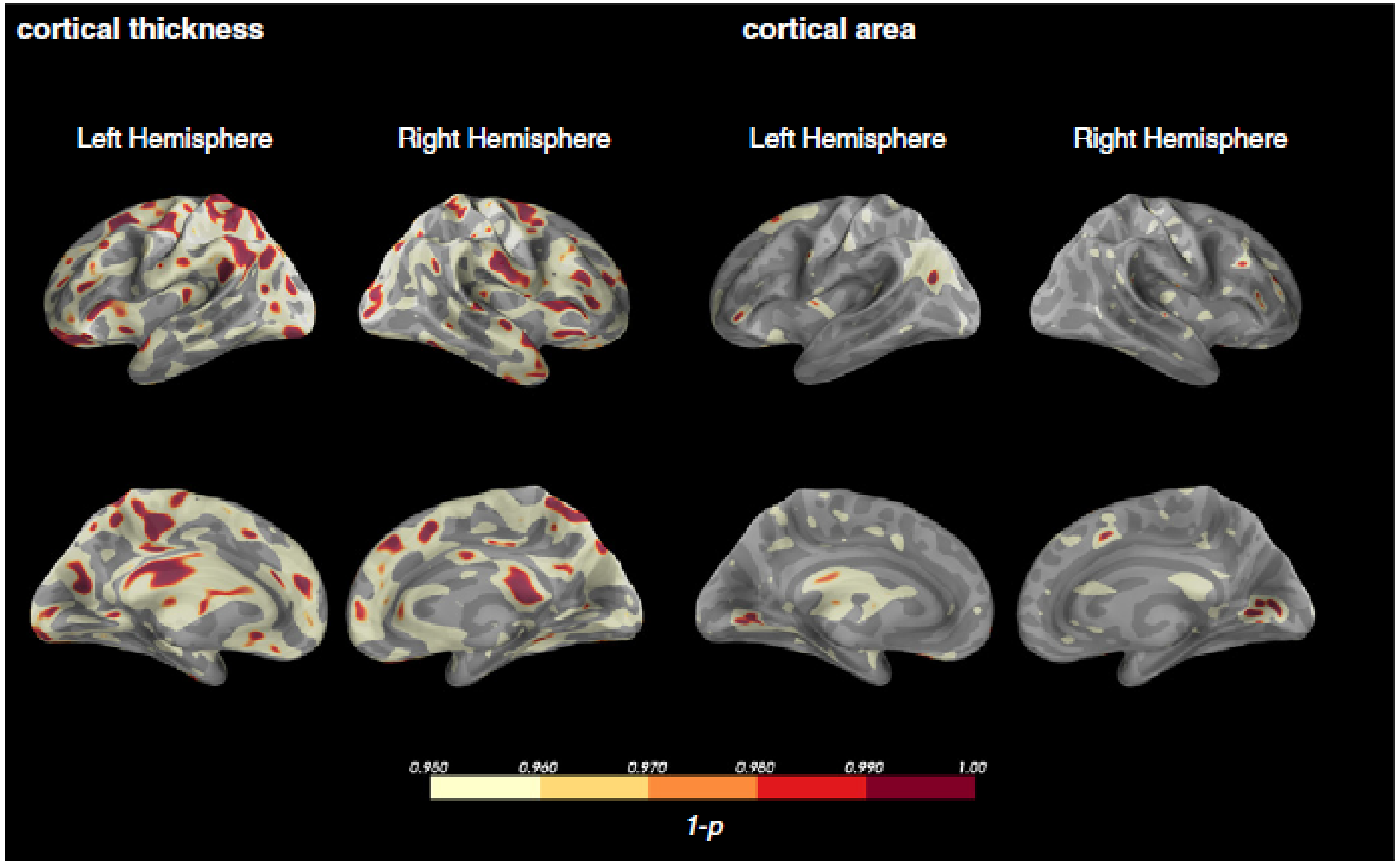
Open Access

RESEARCH ARTICLE

Epilepsy, cognitive deficits and neuroanatomy in males with *ZDHHC9* mutations

Kate Baker[1,2], Duncan E. Astle[2], Gaia Scerif[3], Jessica Barnes[2], Jennie Smith[4], Georgina Moffat[4], Jonathan Gillard[5], Torsten Baldeweg[6] & F. Lucy Raymond[1]

ZDHHC9-associated XLID: Cortical morphometry



ELSEVIER
NeuroImage: Clinical
journal homepage: www.elsevier.com/locate/ynicl
NeuroImage: CLINICAL

Structural brain abnormalities in a single gene disorder associated with epilepsy, language impairment and intellectual disability

Joe Bathelt[a,*], Duncan Astle[a], Jessica Barnes[a], F. Lucy Raymond[b], Kate Baker[a,b]

[a]MRC Cognition & Brain Sciences Unit, Cambridge, United Kingdom
[b]Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, United Kingdom

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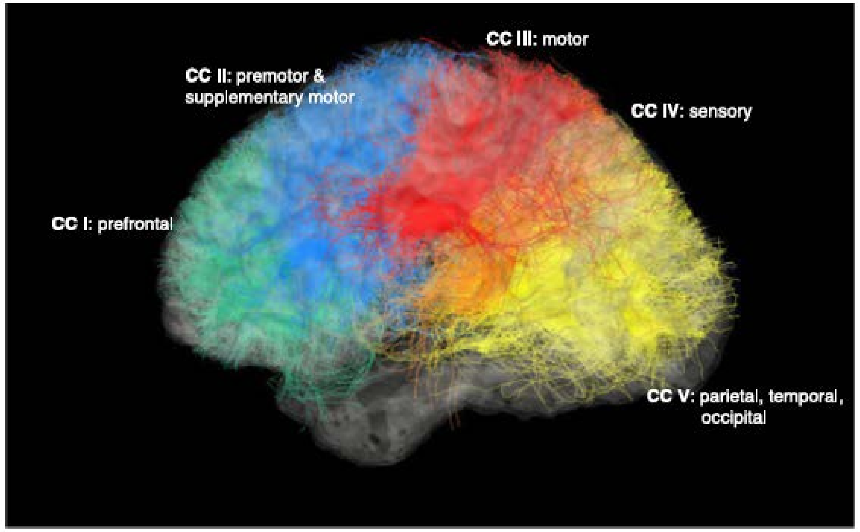
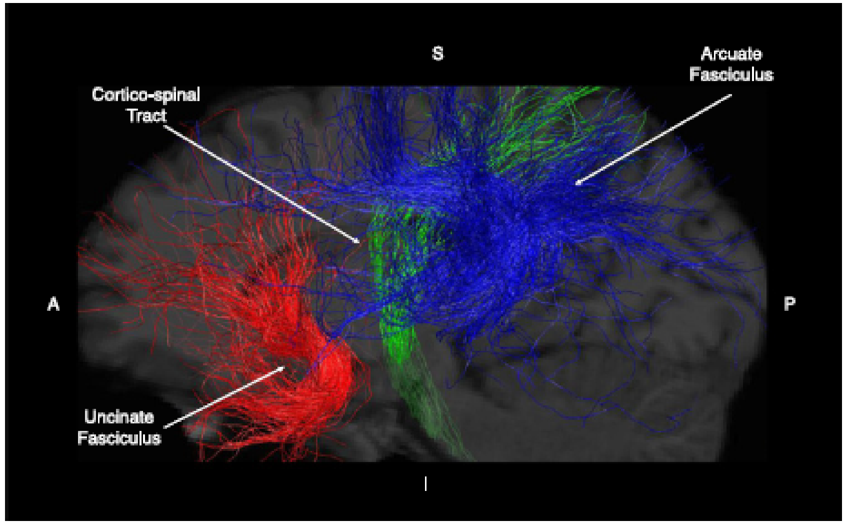
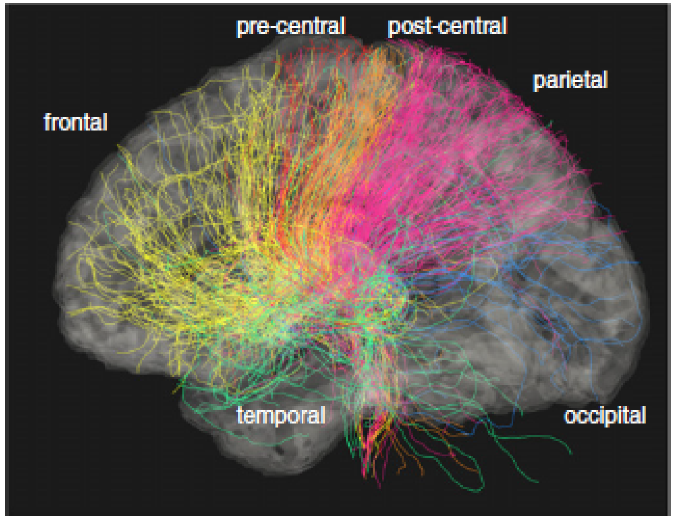
ZDHHC9-associated XLID: tractography



Reduced FA, increased MD / RD:
CC I, CC II, **CC III**



Reduced FA, increased MD / RD:
Right and left arcuate fasciculus
Right and left uncinate fasciculus
No differences in CST



Reduced FA, increased MD / RD:
Right and left precentral and
temporal thalamic projections only

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NeuroImage: Clinical
journal homepage: www.elsevier.com/locate/ynicl

Structural brain abnormalities in a single gene disorder associated with epilepsy, language impairment and intellectual disability

Joe Bathelt[a,*], Duncan Astle[a], Jessica Barnes[a], F. Lucy Raymond[b], Kate Baker[a,b]
[a]MRC Cognition & Brain Sciences Unit, Cambridge, United Kingdom
[b]Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, United Kingdom

ZDHHC9-associated XLID: Structural connectome

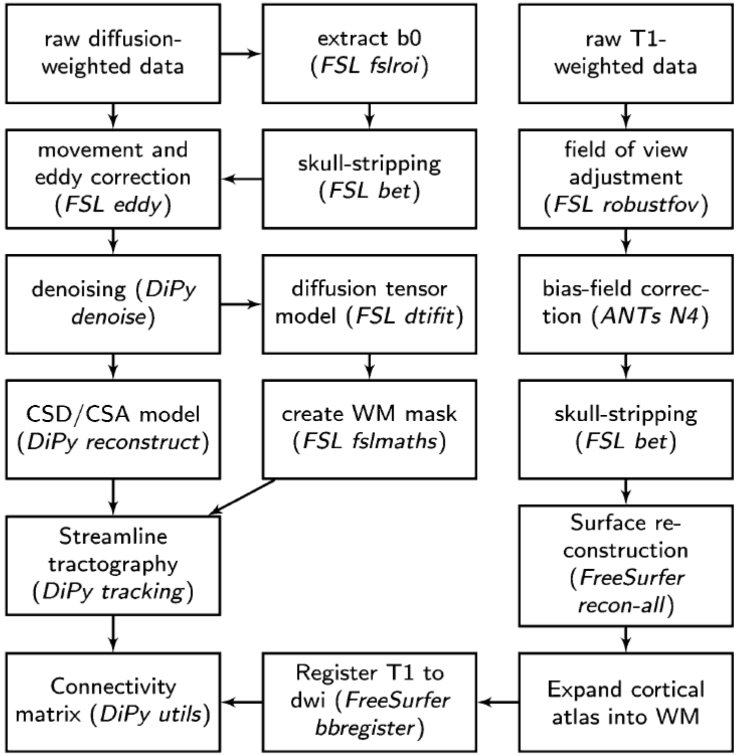
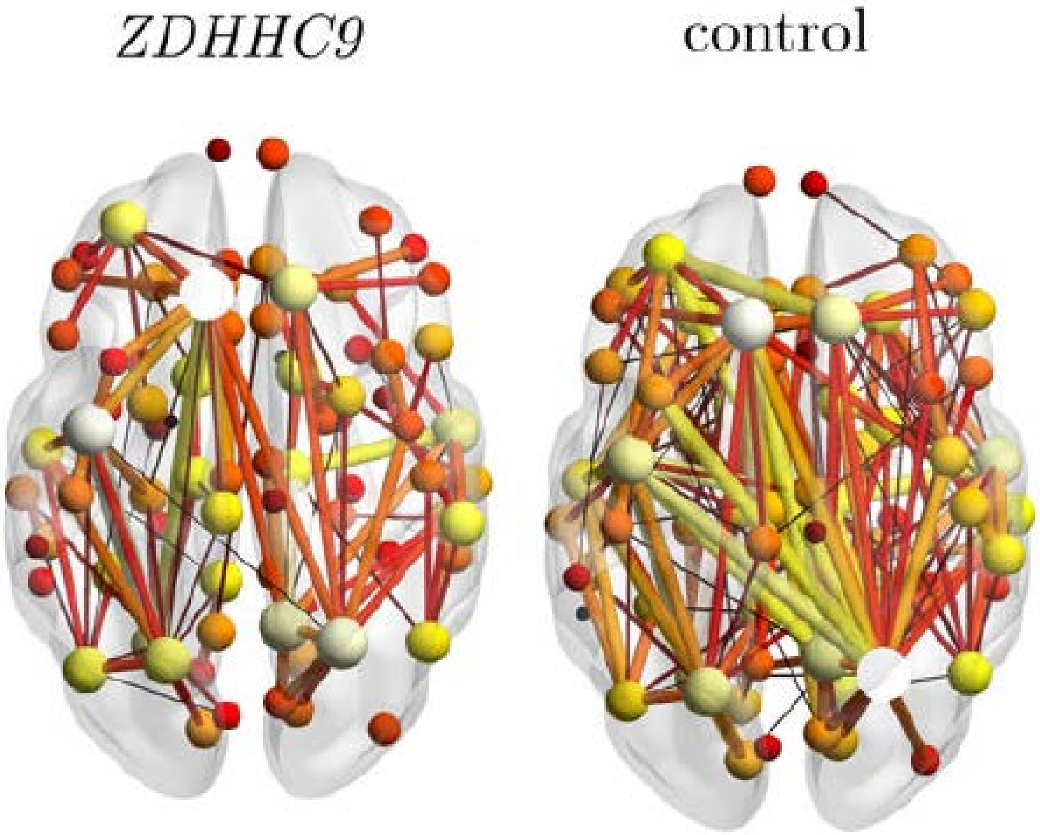


Figure 1. Overview of the processing steps to derive the diffusion-weighted structural connectome.



Cerebral Cortex, July 2017;27: 3806–3817

doi: 10.1093/cercor/bhx027
Advance Access Publication Date: 7 February 2017
Original Article

ORIGINAL ARTICLE

Global and Local Connectivity Differences Converge With Gene Expression in a Neurodevelopmental Disorder of Known Genetic Origin

Joe Bathelt[1], Jessica Barnes[1], F Lucy Raymond[2], Kate Baker[1,2,†] and Duncan Astle[1,†]

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ZDHHC9-associated XLID: Structural connectome

Global reductions in

all FA-based graph metrics

- Node degree
- Node strength
- Clustering co-efficient
- Local efficiency

3814 | Cerebral Cortex, 2017, Vol. 27, No. 7

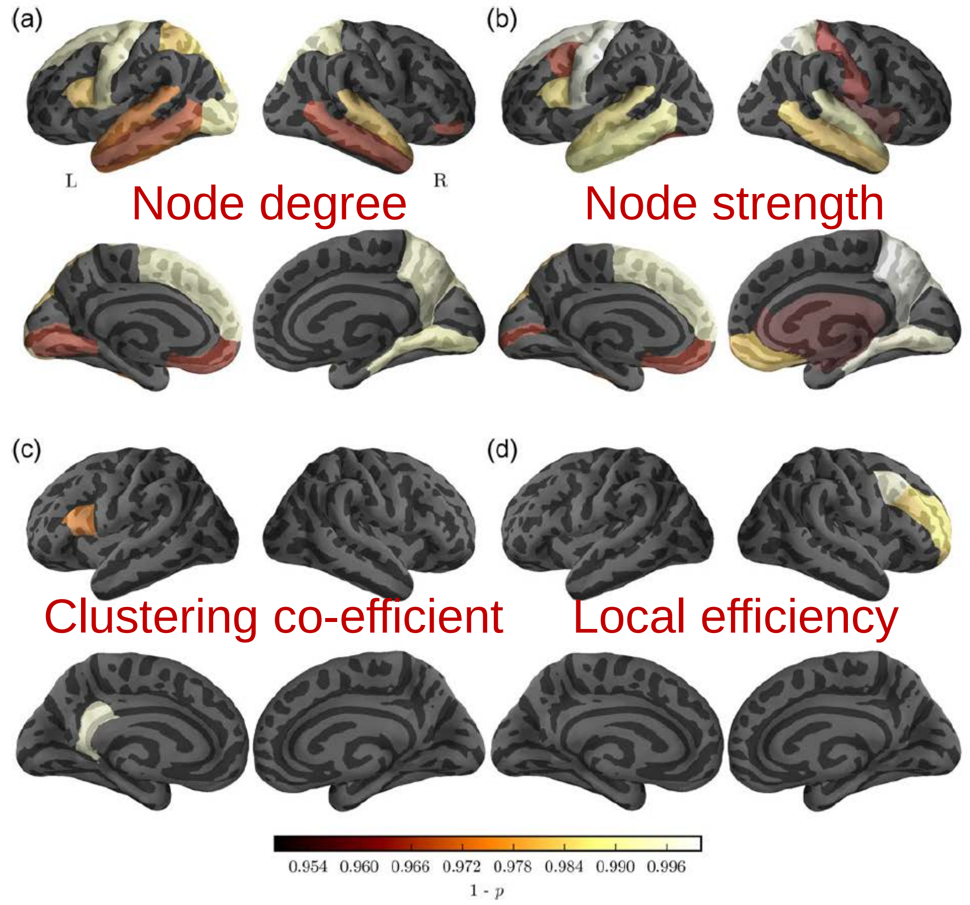

Figure 5. Comparison between the *ZDHHC9* and control group in node measures of (*a*) node degree, (*b*) node strength, (*c*) clustering coefficient, and (*d*) local efficiency. The maps show P-values of paired-sample t-tests corrected for multiple comparison using false discovery rate (FDR).

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ZDHHC9-associated ~~XLID~~ RE and DLD

How is brain ~~development~~ structure and function altered?

How does this relate to communication difficulties?

How does this relate to ZDHHC9 expression?

Prediction from RE literature = we won’t find anything much

- Subcortical and CC volume reductions
- Cortical thickness reductions
- Extensive reductions in WM integrity
- Connectomic differences converging with typical *ZDHHC9* expression

ZDHHC9-associated ~~XLID~~ RE and DLD

How is brain ~~development~~ structure altered?

- Subcortical and CC volume reductions
- Cortical thickness and WM integrity reductions
- Connectomic differences converging with *ZDHHC9* expression
- Small case control study = multiple observations on small n with wide age range
- Rarity = impossible to replicate? Adding more subjects would be non-independent, biased.
- Multiple specificity problems
  - Comparing to high IQ group, not low IQ, language disordered, other genes, RE general, RE other causes…
  - Genotype vs phenotype
- Structure-function relationships are opaque
  - Cannot separate cause from consequence (language acquisition vs skill; language vs other abilities)
- Cross-disorder case control designs?
- Within-sample dimensional and brain-cognition analyses?
- Integrate with developmental cohort data?

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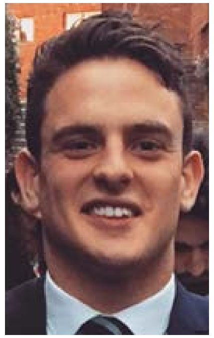
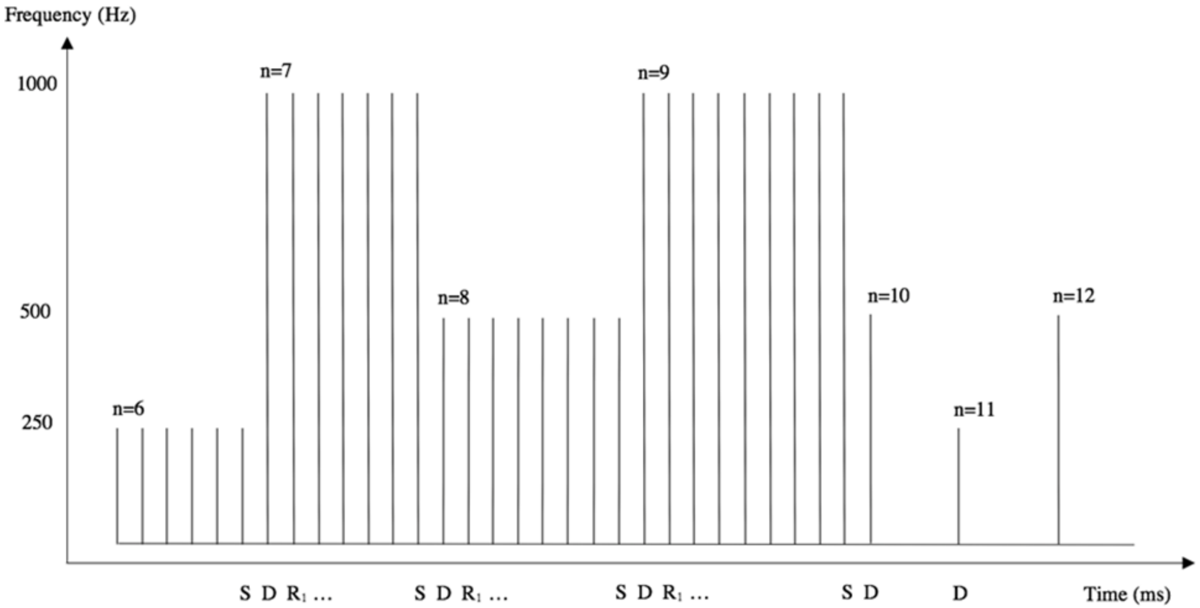
ZDHHC9-associated XLID: MEG



1. Resting state acquisition (2 x 6 minutes)
2. Passive auditory roving oddball acquisition (2 x 6 minutes)



The stimulus sequence consisted of stimulus trains of a random variable number, indicated by variable n (from 6 to 12 repetitions) of identical standard stimuli (indicated by vertical lines) within trains. The frequency varied randomly (between 250Hz, 500 and 1000Hz) from train to train, as indicated by the different height of the vertical lines. Tone lengths were 50ms, with inter-tone intervals of 500ms. S = preceding stimulus to deviant. D = Deviant. R1= Repeat 1.

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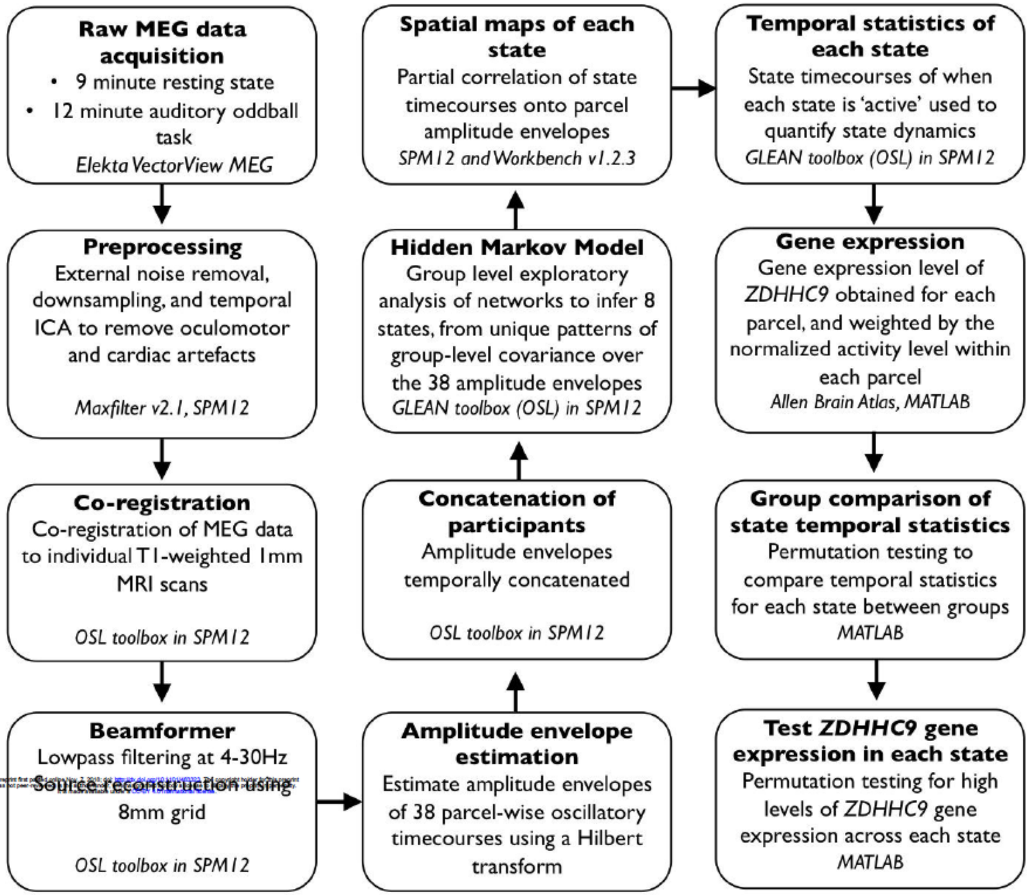
ZDHHC9-associated XLID: MEG networks and HMM



RESEARCH ARTICLE

Functional network dynamics in a neurodevelopmental disorder of known genetic origin

Erin Hawkins[1] | Danyal Akarca[1] | Mengya Zhang[1] | Diandra Brkić[1] | Mark Woolrich[2] | Kate Baker[1,3] | Duncan Astle[1]

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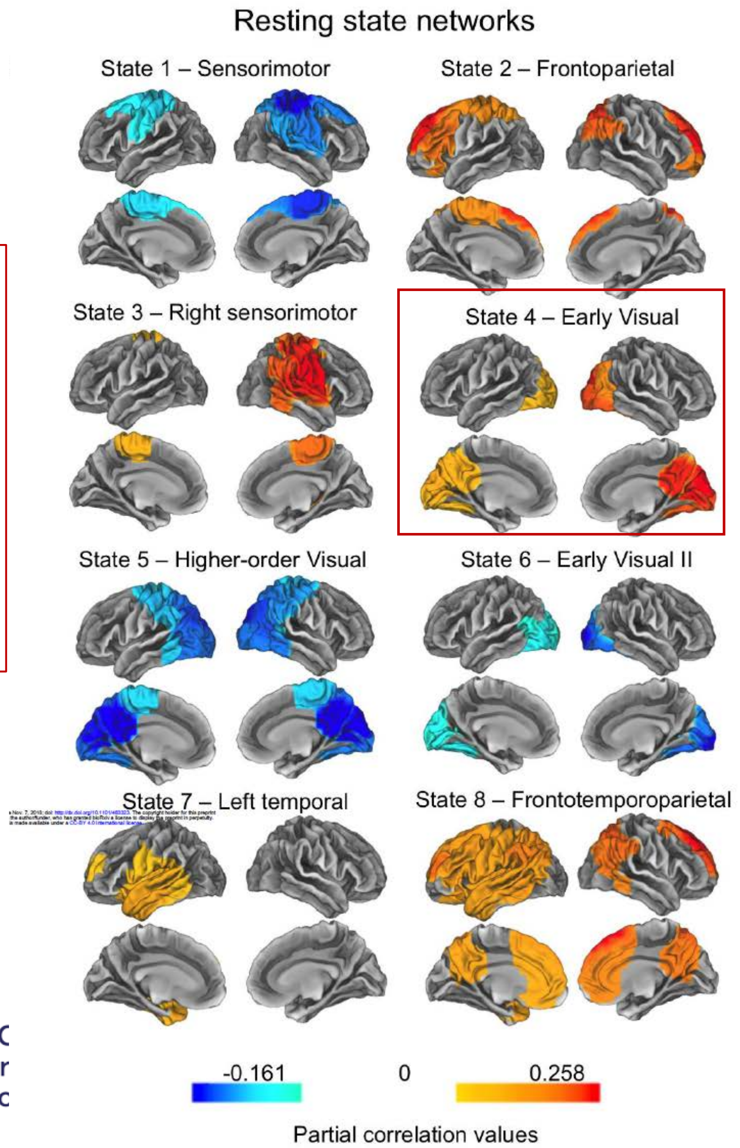
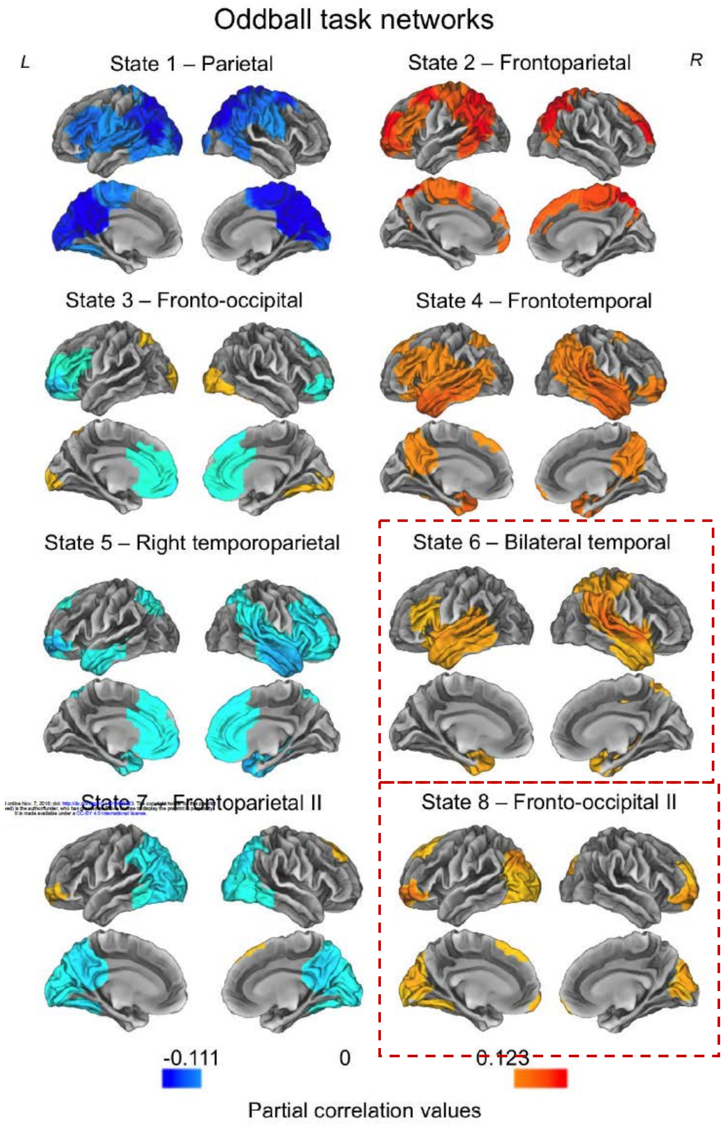
ZDHHC9-associated XLID: MEG networks

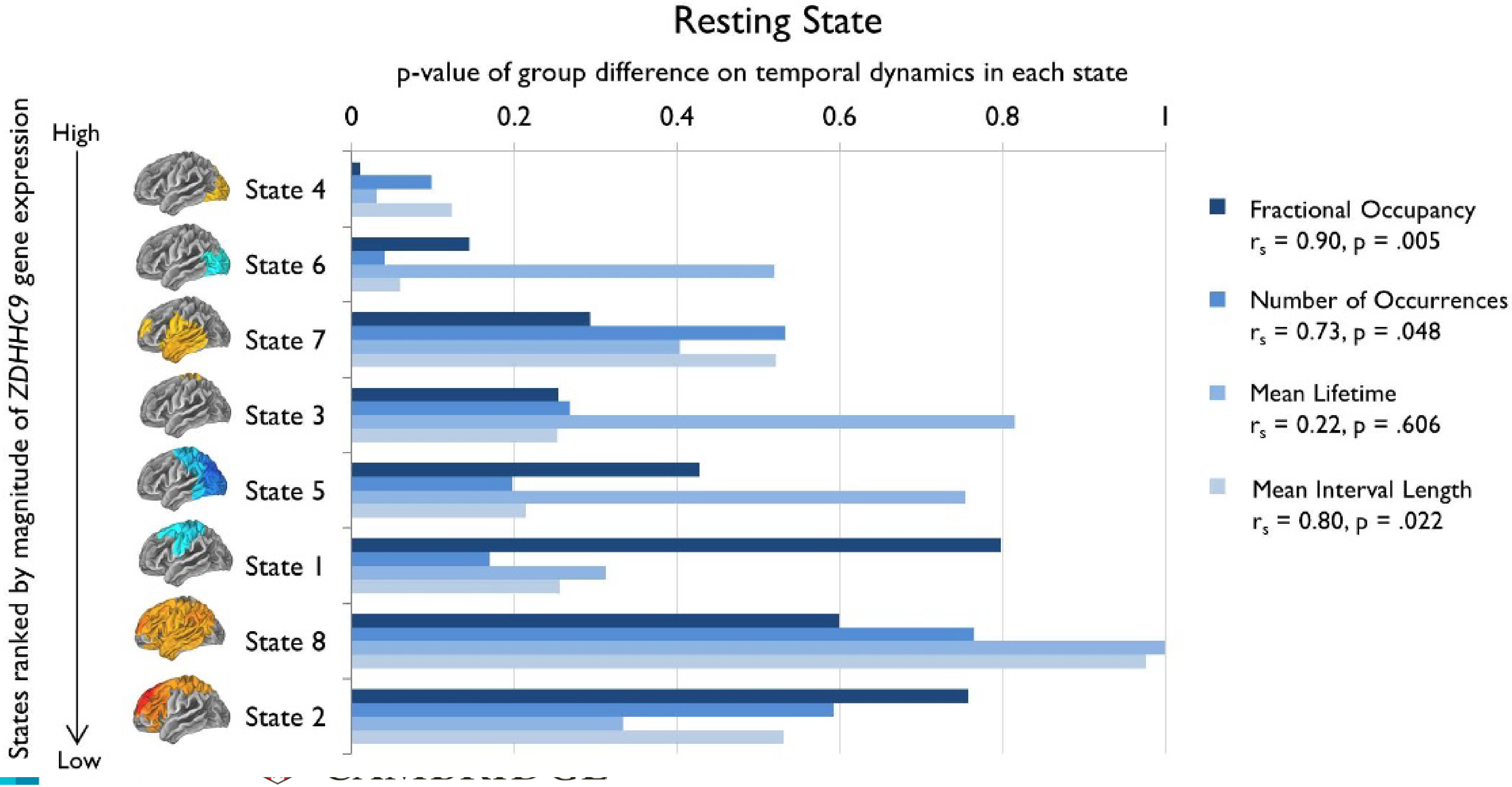
Higher fractional occupancy and mean lifetime in *ZDHHC9* subjects



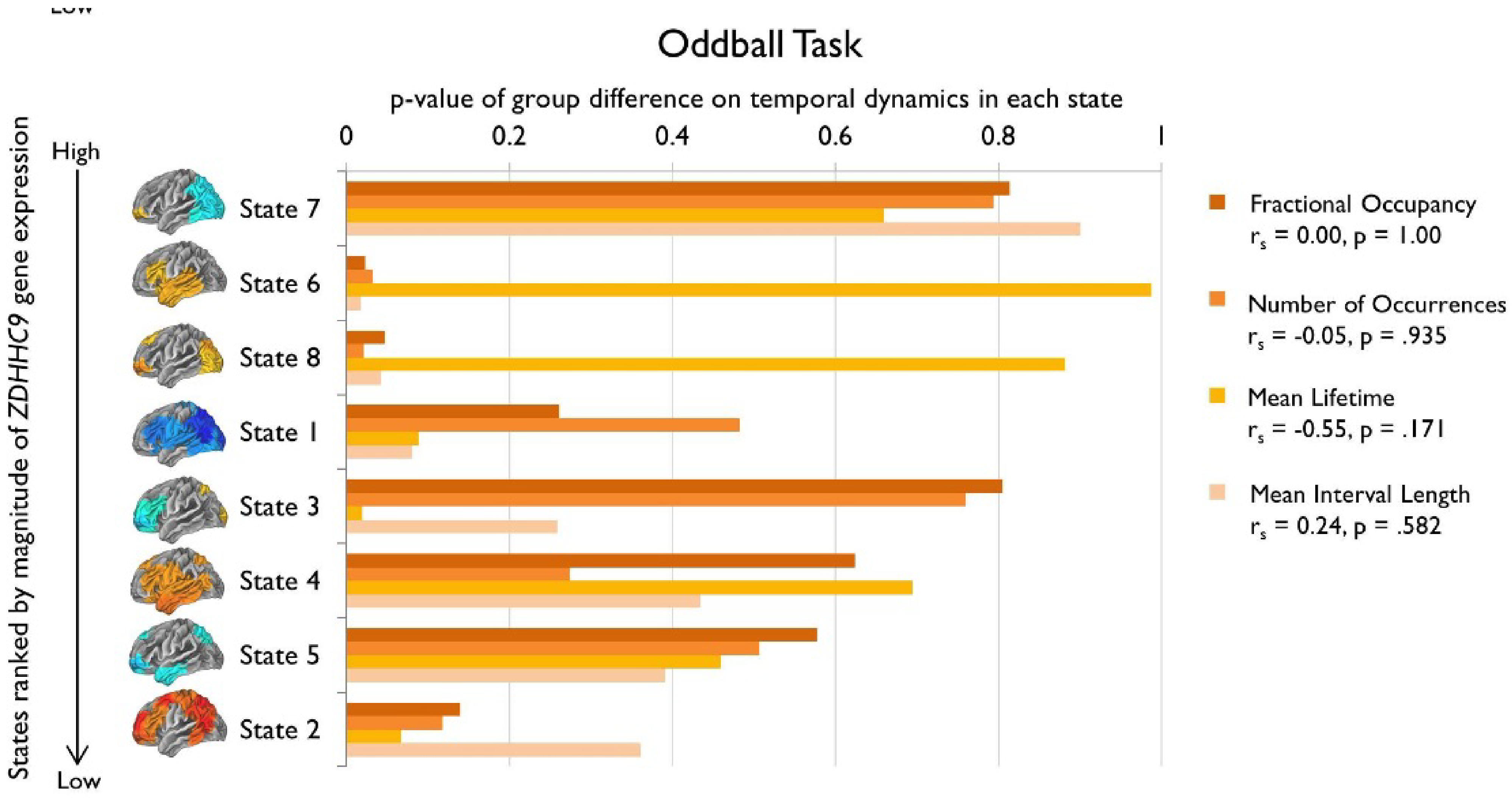


Reduced fractional occupancy, number of occurrences and mean interval length

ZDHHC9-associated XLID: MEG networks



ZDHHC9-associated XLID: MEG networks



ZDHHC9-associated XLID

How is brain ~~development~~ function altered?

- Same functional networks present in cases / controls
- Resting state – limited dynamic differences, correlating with expression topography
- Oddball networks – dynamic differences appear phenotype-relevant, RNN model can recapitulate group differences and is sensitive to loss of inhibition
- All the same general limitations as MRI re N and comparison groups
- Dynamic network and RNN analysis is new – we don't know what to expect across different developmental conditions

ZDHHC9-associated XLID: progress

How is brain ~~development~~ structure and function altered?

How does this relate to communication difficulties?

How does this relate to ZDHHC9 expression?

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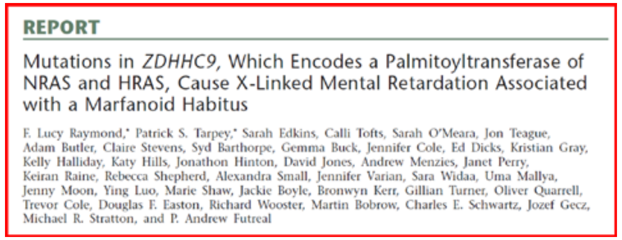
ZDHHC9-associated XLID: progress


REPORT

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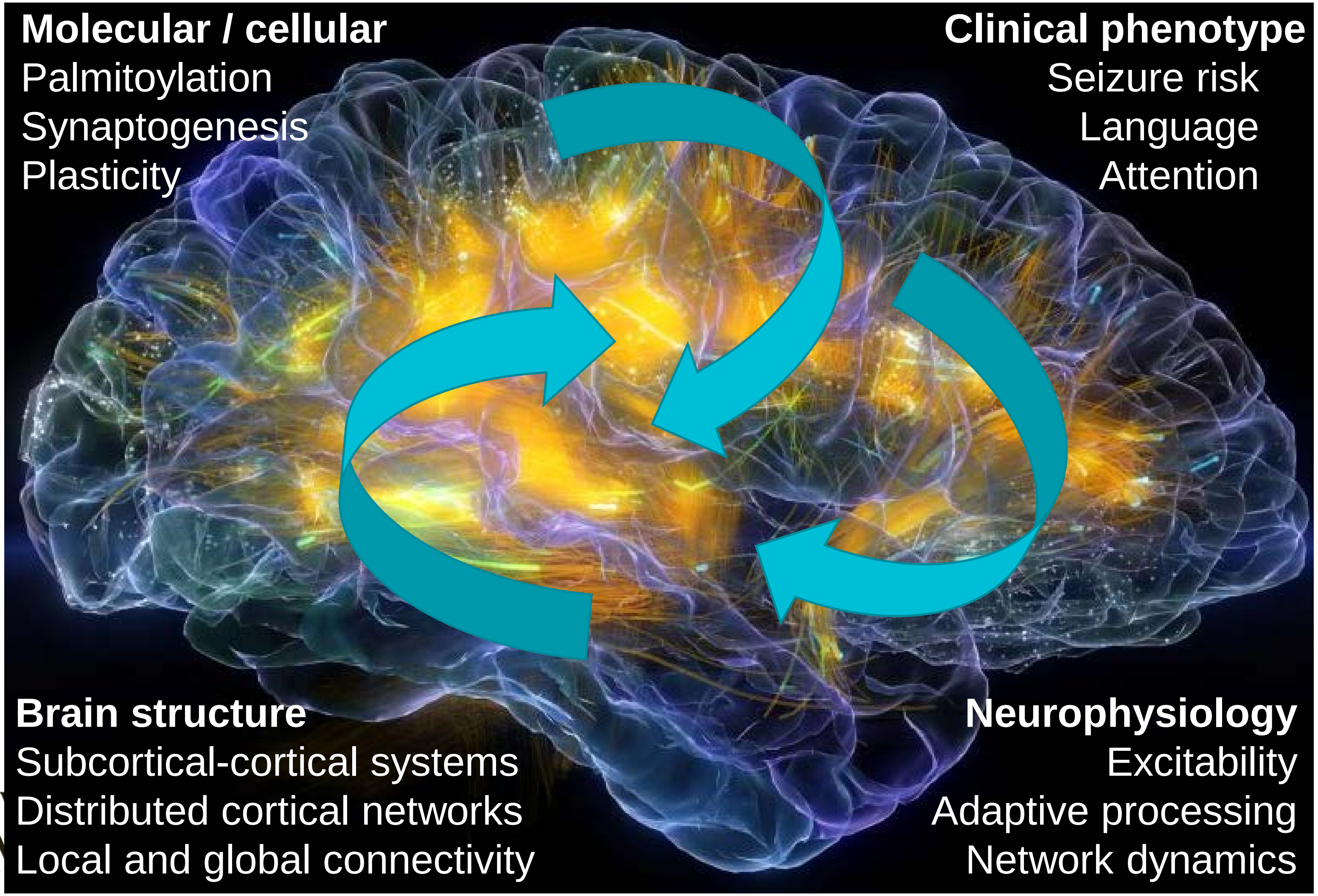

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4. Ideas for future directions

How is brain ~~development~~ structure and function altered?

How does this relate to communication difficulties?

How does this relate to ZDHHC9 expression?

How to integrate?

Developmental and cognitive mechanisms?

Clinically useful?

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Gaia Scerif, Oxford


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Torsten Baldeweg, UCL ICH


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Diandra Brkic, CBU


Danyal Akarca, CBU


Erin Hawkins, CBU

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NHS National Institute for Health Research

The Academy of Medical Sciences

newlife foundation for disabled children

The Baily Thomas Charitable Fund